TESTICULAR BIOPSY IN THE DIAGNOSIS AND TREATMENT OF STERILITY IN THE MALE*

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THE persistent absence of spermatozoa from the semen denotes absolute sterility in the male. This condition requires that either no substantial number of spermatozoa is being formed, or that an obstruction or defect exists which prevents the escape of the cells from the seminal tract. Certain clinical guides are helpful in determining which factor is the cause. Thickened epididymes favor occlusion, while atrophic testicles indicate that the germinal epithelium is deficient. It has become increasingly apparent, however, that azoospermia may be associated with genitalia which are normal to external examination. Accordingly, there is a real need for an accurate way to determine whether the lack of spermatozoa is due to aspermatogenesis or occlusion. A correct diagnosis is obviously essential to proper management, for an occlusion calls for reëstablishment of the patency of the ductal systems, whereas incomplete spermatogenesis theoretically demands that some agent or set of agents be supplied to motivate spermatogenesis.

It has been said that one good diagnosis is worth ten haphazard treatments. The use of testicular biopsies bears out this adage in the problem of the sterile man. The study of testicular tissue has proven to be a reliable and practical method in accounting for the absence of sperm in the semen, and promises to minimize errors in treatment.[1] The tissue likewise affords a new source of information relative to the histopathology of the human testes and may assist in clarifying some of the fundamental clinical concepts of seminal deficiencies.

The procedure of obtaining the biopsy requires no special skill and entails little discomfort and incapacitation. The genitalia are prepared for operation and a small area in the scrotal skin is anesthetized with

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1 per cent novocaine. An incision is made and carried down through the tunica vaginalis. A pair of ocular palpebral retractors is inserted, and the tunical albuginea is exposed. A small "V" shaped incision is made therein and a minute piece of testicular tissue is excised. Silk or fine plain gut sutures are used to arrest hemorrhage and approximate the layers of the wound. The operation is repeated on the opposite side. A suspensory is applied and the patient is sent home from the operating room. The tissue is fixed in Bouin's solution and sections are prepared in the usual manner.

Two main classes of testicular tissue are found.[2] The seminiferous tubules may contain either normal or defective germinal epithelium. The degree of cellular activity varies considerably in different tubules in each section, but the general contrast is striking and offers little chance for serious confusion. Several types of defective germinal tissue may be seen. The biopsy specimens from some men with normal sized testicles exhibit spermatic cells which have progressed to the spermatid stage, just short of full maturity. Others have germinal epithelium which is arrested at an early stage of spermatogenesis. A third type have tubules almost devoid of germinal epithelium, and their lumens may be filled with hyaline. A fourth type of abnormal testes is characterized by extraordinary proliferation of fibrous tissue about the tubules. Sections of testes associated with occlusion of the efferent seminal tracts have, in main, well-organized germinal epithelium with many mature spermatozoa.

The clinical usefulness of the biopsies is quite apparent. Active normal spermatogenesis requires no stimulating agents. Complete degeneration of the germinal tissue defies treatment with substances now available. Thus, useless or misapplied therapy is avoided and an approach to rational treatment is made.

The mandates of successful treatment of sterility, however, include more than a mere consideration of the histopathology of the testes. Three essential criteria are involved. They are:

1. The primary cause of the disturbance must be recognized and evaluated.
2. Specific and potent therapeutic agents must be available and assimilable.
3. The end organ must be refractory.

Lack of knowledge of certain important facts concerned with these

three criteria accounts for the generally unsatisfactory state of therapy at this time. It may be appropriate to examine these principles in the light of present developments to evaluate current and future modes of the clinical treatment of impaired fertility.

It is likely that faulty spermatogenesis can be assigned as due to one of four causes. The identity of the particular cause is probably the key to effective therapy.

1. An inherited gametogenic factor may account for sterility in man. As yet there is no clinical proof of this theoretical possibility, but other species furnish notorious examples of this genetic phenomena. The mule, which is a hybrid animal, is always sterile. There is no possibility of revoking chromosome patterns, and treatment is futile.

2. A second cause of spermatogenic failure may be some deficiency disease. This is clearly indicated by the effect of inadequate diets in experimental animals.[3] The work of Dr. John MacLeod[4] has demonstrated the necessity of certain foodstuffs, enzymes, and vitamins to the life processes of spermatozoa. The needs of the germinal epithelium may not be dissimilar to the requirements of sperm.

Subclinical or mild deficiency states are now recognized as established clinical entities, and subsequent investigations may reveal that defective spermatogenesis is linked with an inadequate vitamin supply or, more likely, to a failure to absorb and utilize these and other substances.[5, 6] The past and present clinical experience with corrective dietary regimes and vitamin medications have not been singularly encouraging. Future advances may reverse present attitudes, and it is possible that certain cases of infertility due to deficiencies will be corrected and cured.

3. There is no doubt that the gonads are intimately linked with the other glands of the endocrine system.[7] Nearly thirty years ago it was shown that removal of the pituitary caused prompt atrophy of the germinal epithelium. Since then an enormous amount of interest has been displayed in the relationship of the reproductive glands to the other endocrines. The clinical application of endocrine therapy in man has borne far less brilliant results than some of the experimental animal work. There are a number of well authenticated reports which illustrate effective treatment of impaired fertility in men with endocrine products but the failures are far more common than the successes. The deserving skepticism is well understood when it is realized what great

obstacles still remain in therapeutic pathways. Species vary greatly in their responses to endocrine substances so that much of the experimental work on animals and birds cannot directly be transferred to the human with the assumption that it is applicable. We have no simple tests to evaluate or diagnose subclinical or minor grades of endocrinal disorders. The therapeutic products which are available are not specific and probably far below basic requirements of actual need. These and many related problems await clarification before the dreams of a "specific hormone" for spermatic tissue will be available in the same sense that insulin is used for diabetes.

4. A fourth class of disturbances which may alter spermatogenesis may be grouped under the term "constitutional and local disorders." It is evident that the testicles are labile structures and are sensitive to certain generalized alterations of body function. It is known that debilitating illnesses will arrest spermatogenesis. Artificially induced fever will cause transient injury to the germinal layers.[8] Much speculation is given to the effect of less definite influences such as fatigue, nerve strain, overwork, alcohol and minor illness. It may well be that subnormal semen is much more adversely affected by these factors than are specimens of high quality. These agents may then resolve themselves into individual considerations which have relatively little effect on the very fertile, yet are especially harmful to those less generously endowed. The various diseases of the genitalia are adequately described in text books and the influences on fertility are well known. The biopsies of testicular tissue have revealed, in some instances, marked thickening of the fibrous tissue encircling the seminiferous tubules. An explanation for this is not ventured herewith, but it is conceivable that these deposits may act as barriers and prevent proper nourishment of the germinal epithelium. This affords a probable example of a non-refractory end organ incapable of being stimulated.

No claim is made that the examination of the biopsied testicular tissue will depict which one of these foregoing conditions has caused aspermatogenesis. The inconsistent results of treatment are more fully appreciated, for response depends on: the identification of the cause, the use of appropriate corrective agents, and the ability of the testes to respond to such stimulation. Testicular biopsies will not solve all these problems, but will obviate some of the difficulties. The information gained from the biopsy will certainly prevent some men from re-

ceiving innumerable injections of hormones when the testes are proven to harbor large numbers of spermatozoa, or are atrophic to a hopeless degree. A selection of favorable cases for treatment is made possible and a reasonable trial is given to substances purported to have therapeutic value.

Occlusions in the seminal passageways, as well as faulty spermatogenesis, may cause absolute sterility in men. The majority of acquired obstructions are located in the lower portions of the epididymes or beginning of the vasa. Two cases of congenital absence of the vasa have come under my care during the past two years. Notwithstanding the fact that a normal outlet for spermatozoa had never been available, the testicular biopsies demonstrated fairly normal spermatogenesis. The ability of the testicles to maintain their function despite years of obstruction is in harmony with the theories that the epididymes are capable of absorbing and disposing of spermatozoa. These organs, rather than the seminal vesicles, are perhaps the true "graveyards of the spermatozoa." This cyclic process of production and absorption may account for the entire absence of sperm in the semen even though a few mature sperm are seen in some biopsies showing faulty and poor spermatogenesis.

Clear indication for operation is afforded by the aid of biopsies. An obstruction or congenital anomaly of the efferent tract is to be inferred if several ejaculates have no sperm yet the biopsy shows well-differentiated germinal epithelium with many mature spermatozoa.

A second operation is then performed and a full exposure of the scrotal contents is obtained. The patency of the vas is tested by injecting a fluid into its lumen at a level with the body of the epididymis. The epididymis is punctured at a corresponding point and the expressed secretions are examined immediately for sperm. If the vas is patent and sperm are found a union of the two structures is formed after the method which Martin described forty years ago. Arterial silk sutures serve as excellent material for the juncture of vaso-epididymal anastomosis. If patency is established, sperm will appear in the ejaculate within 12 months. Failures are due to inability to complete the operation because of extensive obstructions along the vas, or subsequent postoperative closure of the fenestra between the vas and epididymis. The operation may also fail to bring clinical results for, although at least one tract has been opened, too few or immotile sperm are ultimately secured in the semen. Successful results should reach about 20 per cent of those operated

upon, and yet the failures are no worse off than prior to operation. In retrospect, it may be said that all too often such men are dismissed as hopeless and that, if they are willing to accept unfavorable odds, the operation deserves trial.

Summary

External examination of the male genitalia does not always indicate the state of spermatogenesis or condition of the epididymes and vasa. Testicular biopsy is a practical method of appraising the value of the spermatic tissue. Appropriate treatment can be applied and useless therapy avoided. The inconsistent results of treatment of grave disorders of the germinal epithelium are commensurate with the existing etiological and therapeutic problems, but future research promises much for the development of efficient treatment.*

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* Six case histories with microphotographs, illustrating the usefulness of testicular biopsies, were included in the original presentation of this paper.